Hanna M, O'Brien C, Wilson MC. Prolonged-release oxycodone enhances the effects of existing gabapentin therapy in painful diabetic neuropathy patients. Eur J Pain 2008;12:804-813.

Design: Randomized clinical trial

Population/sample size/setting:

- 328 patients (210 men, 110 women, mean age 60) treated for painful diabetic neuropathy at 70 sites across Europe and Australia
- Eligible patients had at least 3 months of diabetic neuropathy pain as assessed by the Michigan Neuropathy Screening Instrument (MNSI) score of 2.5 or greater, were taking gabapentin at a maximum tolerated dose, and were having current pain of at least 5 on a scale from 0-10, with HbA1c <=11
- Exclusion criteria included taking any opioid in the past month, or previous use of oxycodone in combination with gabapentin

Main outcome measures:

- All patients continued to take gabapentin throughout the 12 weeks of the double-blind study
- Randomization was to one of two drugs to take in combination with gabapentin: oxycodone sustained release (n=163) or placebo (n=165) to be taken every 12 hours
- Starting dose of both study drugs was 5 mg, which could be titrated upwards throughout the 12 weeks of the study; up to a maximum dose of 80 mg/d
- At the end of the study, 5% of the patients in both treatment groups were taking the starting dose of 5 mg q 12 h; 34% of the patients in the oxycodone group reached the maximum oxycodone dose at least once during the study, but 100% of the placebo patients reached the maximum dose at least once
- The most common oxycodone dose (60% of the group) was 20 mg q 12 h; the full dose distribution of oxycodone is not reported
- Attrition was approximately equal in both groups; but the reasons for withdrawal were different
- In the oxycodone group, 74% completed the study; 64% of the withdrawals were for adverse events, and 14% for lack of therapeutic effect; in the placebo group, 78% completed the study, but 54% of withdrawals were for lack of effect and 24% for adverse events
- Main outcome measure was the change from baseline in the pain scores, measured at 6 separate times during the 12 weeks of the study
- There was an overall advantage of oxycodone over placebo of 0.55 pain score points; the mean change from baseline at the 6th measurement was 2.1 for oxycodone and 1.5 points for placebo
- There was a treatment x period interaction (the advantage of oxycodone over placebo was not apparent in the first period measurement, but the advantage was apparent in the second and subsequent measurements)

- Sleep disturbance, a secondary outcome, showed that patients taking oxycodone had fewer nights of disturbed sleep than placebo, but there was no difference between groups with respect to quality of sleep
- Global assessment of pain relief (good or very good) was reported by 56% of oxycodone patients and by 41% of placebo patients
- When comparing their treatment during the trial with their pre-study treatment, 74% of the oxycodone group rated the study treatment as better or much better; 47% of the placebo group had the same response
- Treatment-related adverse effects were more common among oxycodone patients (88%) than among placebo patients (71%); opioid-related effects, such as constipation, nausea, dizziness, fatigue, and somnolence, were the most common adverse effects

Authors' conclusions:

- Adding prolonged-release oxycodone to gabapentin provides an important improvement in analgesia compared to gabapentin alone, and the combination of both drugs is likely to be beneficial for diabetic neuropathic pain
- Although oxycodone appeared safe during the course of the study, long-term use of any opioid should be undertaken with caution

Comments:

- Randomization and allocation concealment appear to be adequate, and the risk of bias is low
- Blinding was not formally assessed, but the occurrence of opioid-related side effects is likely to unmask the assigned drug for at least some patients
- The effect difference between oxycodone and placebo appears to be modest, but the placebo response rate was high, which can reduce the apparent treatment difference between a study drug and its placebo comparison
- Gabapentin dosage was evenly distributed between the groups, but the study design was to keep patients on their entry dose of gabapentin, precluding the study from finding out if the addition of oxycodone to gabapentin allows the dose of the latter to be adjusted downwards
- The observed period by treatment interaction (oxycodone not superior to placebo in the first period but superior in later periods) was very likely due to the titration of the dosing, with the starting dose of 5 mg q 12 h not superior to placebo for most patients

Assessment: adequate for evidence that prolonged-release oxycodone may provide additional analgesia for neuropathic pain when added to gabapentin